REMARKS

Claims 1, 4 and 11 have been amended. No new claims have been added. Accordingly, claims 1-20 are currently presented for examination.

No new matter has been added to the application. Claims 1, 4 and 11 have been amended to each include a specific wherein clause which recites that cellular proliferation is inhibited. Support for the amendments to claims 1, 4 and 11 can be found at page 31, line 20 to page 32, line 15 (Examples 1 and 2) and Tables 1 and 2.

Objection to the Specification

The specification of the instant application is objected to because it contains embedded hyperlinks at page 19, lines 14 and 29. The Examiner has requested that Applicants delete all browser executable code contained within the application.

Applicants have searched the specification and found only the two instances of browser executable code which have been cited by the Examiner. In the first instance, which is located at page 19, line 14, the sentence containing the browser executable code has been deleted. In the second instance, which is located at page 19, line 29, Applicants have replaced the hyperlink with text that teaches the public how to access the intended website by using a web browser. Since the amendment causes the text of the hyperlink to be physically separated, the text no longer constitutes browser executable code.

In view of the above amendments, Applicants respectfully request the Examiner to withdraw his objection to the specification.

Claim Rejections Based on 35 U.S.C. § 112, second paragraph

Claims 1-20 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner asserts that the rejected claims, which are drawn to methods of inhibiting cellular proliferation, each lack an active step requiring that cellular proliferation actually be inhibited. Additionally, the Examiner asserts that claim 11 is indefinite because it appears to claim methods which use more than one gene even though only a single SEQ ID NO: is recited.

Applicants have amended each of the pending independent claims (claims 1, 4 and 11) to recite that cellular proliferation is actually inhibited. Additionally, as suggested by the Examiner, claim 11 has been amended to remove the phrase "one of" immediately prior to "SEQ ID NO: 165." In view of these amendments, Applicants believe that claims 1-20 are not indefinite. Accordingly, Applicants respectfully request that the Examiner withdraw his rejection of claims 1-20 based on 35 U.S.C. § 112, second paragraph.

Claim Rejections Based on 35 U.S.C. § 112, first paragraph with Respect to Written Description

Claims 1-20 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors possessed the claimed invention at the time the application was filed. In particular, the Examiner asserts that each of the claims are drawn to methods of inhibiting cellular proliferation that encompass compounds for which there is no written description.

Applicants respectfully submit that claims 1-20 are adequately described in the specification of the instant patent application. Applicants note that they were the first to determine that the polypeptide of SEQ ID NO: 325 (encoded by the gene of SEQ ID NO: 165) is involved in cellular proliferation. Applicants further demonstrated that two antisense nucleic acid complementary to a portion of SEQ ID NO: 165 inhibit the proliferation of at least four different organisms. Applicants maintain that the identification of the biological role of a protein coupled with a demonstration that inhibiting the activity or reducing the amount of the protein or a nucleic acid encoding the protein inhibits cellular proliferation is sufficient to support claims directed to inhibiting cellular proliferation by inhibiting the activity or reducing the amount of the protein or a nucleic acid encoding the protein. In particular, Applicants maintain that where one is the first to identify the biological role of a protein and one has demonstrated the biological consequences of inhibiting its activity or reducing its amount, 35 U.S.C. §112 does not require the disclosure of all possible compounds which may be used to inhibit the activity or reduce the amount of the protein in order to support claims directed to methods for achieving the demonstrated biological effect by inhibiting the activity or reducing the amount of the identified protein or a nucleic acid encoding the identified protein.

Furthermore, while Applicants realize that actions taken by the P.T.O. in other patent applications are not binding on the P.T.O. with respect to the present application, Applicants note that a number of patents which claim the use of a generic class of compounds to achieve a particular biological effect have issued where the applicants were the first to appreciate that compounds which act via a particular mechanism are capable of achieving that effect. Although Applicants found many instances of such patents, U.S. Patent Nos. 6,506,774, 6,518,245, 6,528,518 and 6,545,048 are provided herewith as exemplary patents. Each of these patents contains claims to the use of a generic class of compounds which inhibit certain biological molecules to achieve a particular biological effect even though they exemplify only a few compounds within the generic class. Accordingly, Applicants maintain that the requirements of 35 U.S.C. §112, first paragraph, are satisfied with respect to the presently claimed methods of inhibiting cellular proliferation by reducing the amount or activity of the polypeptide of SEQ ID NO: 325 or a nucleic acid encoding the polypeptide.

In addition to the foregoing, Applicants have provided specific disclosure that satisfies the written description requirement. In the instant application, Applicants are claiming methods of inhibiting cellular proliferation by inhibiting the activity or reducing the amount of polypeptide of SEQ ID NO: 325 or a nucleic acid encoding the polypeptide of SEQ ID NO: 325 (claims 1-10, 18 and 19) and methods of inhibiting cellular proliferation by providing a compound with activity against a gene corresponding to SEQ ID NO: 165 or a product thereof (claims 11-17 and 20). As discussed in detail below, Applicants have described a number of methods of inhibiting cellular proliferation by inhibiting the activity or reducing the amount of a polypeptide of SEQ ID NO: 325 (WaaE) or its corresponding gene as well as methods of inhibiting cellular proliferation by providing a compound with activity against a gene corresponding to SEQ ID NO: 165 (*waa*E) or a product thereof. Applicants have not only provided several specific compounds which inhibit cellular proliferation but they have also provided extensive guidance with respect to methodology which may be employed to identify additional compounds which may be used.

Claims 1-3 and 18 are drawn to methods for inhibiting cellular proliferation by inhibiting the activity or reducing the amount of a WaaE polypeptide (SEQ ID NO: 325) or a nucleic acid encoding the polypeptide. Applicants have demonstrated that particular antisense nucleic acids complementary to the gene encoding the WaaE polypeptide inhibit cellular proliferation.

Applicants have also described a method of identifying additional antisense nucleic acids having activity against the *waa*E gene (SEQ ID NO: 165) and products thereof. In particular, Applicants describe a method for introducing an antisense nucleic acid into a cell and determining the extent of the inhibition of cellular proliferation that results (see Example 1 at page 31, lines 18 to 31). Additionally, the specification at page 24, line 26 to page 25, line 20 describes antisense fragments comprising at least, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400 or 500 consecutive nucleotides of a sequences complementary to SEQ ID NO: 165 or complementary to a nucleotide sequence encoding a protein of SEQ ID NO: 325 which can be used in the method to identify antisense with activity against the *waa*E or its products. Applicants have further described regions of antisense nucleic acids that can be used to make triple helix oligonucleotides that are capable of inhibiting cellular proliferation (see page 105, lines 3-12 and Example 43 at page 107, line 12 to page 108, line 6). Applicants have also disclosed modified oligonucleotide analogs and peptide nucleic acid (PNA) analogs that can be made from any of the described antisense nucleic acids (see page 103, lines 8 to 13 and page 103, lines 14-32, respectively). Applicants have also disclosed a method for screening combinatorial chemical and/or natural product libraries for small molecule compounds that have activity against a WaaE polypeptide or a *waa*E gene (see Examples 8 and 9, pages 67 to 79). In addition to the methods which have been explained above, Applicants have described methods for inhibiting proliferation by inactivating a proliferation-required gene by integrative gene replacement (see page 59, line 11 to page 61, line 31). Additionally, Applicants have described a method of inhibiting cellular proliferation by providing to a host cell, which has a mutant chromosomal copy of an a gene required for proliferation, a single copy of the proliferation-required gene in trans under control of a regulatable promoter. When expression of that gene is "turned off," proliferation of the cell is inhibited (see page 62, lines 8 to 32). Additionally, a skilled artisan, upon reading Applicants' specification, would recognize that each of the above-described techniques can be used to obtain agents which inhibit the activity or reduce the amount of the polypeptide of SEQ ID NO: 325 or a nucleic acid encoding the polypeptide. In view of Applicants discovery that inhibiting the activity or reducing the amount of the polypeptide of SEQ ID NO: 325 or a nucleic acid encoding the polypeptide inhibits cellular proliferation, the demonstration that particular antisense nucleic acids complementary to a portion of the gene encoding the polypeptide inhibit proliferation, and the extensive teachings of methods for obtaining agents which reduce the amount or inhibit the

activity of the polypeptide, Applicants maintain that the requirements of 35 U.S.C. §112 have been satisfied. Claims 4 and 11 and claims dependent thereon are drawn to methods of inhibiting cellular proliferation by providing a compound which inhibits the activity or reduces the amount of the WaaE polypeptide (SEQ ID NO: 325) or its corresponding gene or transcript (claim 4) and methods of inhibiting cellular proliferation by providing a compound with activity against the *waa*E gene (SEQ ID NO: 165) or product thereof (claim 11). As the Examiner indicated in his Office Action, the compounds used in these claims are not limited to antisense nucleic acids. Rather these claims include, but are not limited to, the use of compounds such as small molecules, antisense nucleic acids, triple helix oligonucleotides and other macromolecules. Applicants maintain that, for the reasons discussed above with respect to Claims 1-3 and 18, the requirements of 35 U.S.C. § 112, first paragraph have been met.

The Examiner asserts that with respect to claims reciting the use of antisense nucleic acids to inhibit the activity or reduce the amount of the polypeptide of SEQ ID NO: 325 or a nucleic acid encoding the polypeptide, the written description is not satisfied because Applicants did not provide the structure of a representative number of species which have the recited function. With respect to claims drawn to methods of inhibiting cellular proliferation by providing an antisense nucleic acid or a proliferation-inhibiting portion thereof which inhibits the activity or reduces the amount of a polypeptide of SEQ ID NO: 325 or a nucleic acid encoding this protein (claims 5-7) or which has activity against a gene corresponding to SEQ ID NO: 165 or a product of this gene (claims 12-14), the Examiner is invited to review Example number 15 of the Written Description Training Materials (available at the USPTO website) which is based on and in accordance with the Written Description Guidelines (66 FR 1099, January 5, 2001) promulgated by the USPTO. Example 15 of the Training Materials illustrates a case where the written description of an application supports a claim to broad genus of antisense molecules that inhibit the production of human growth hormone (HGH). In this example, the applicant has disclosed SEQ ID NO: 1 (HGH) and has stated that the invention includes antisense oligonucleotides complementary to SEQ ID NO: 1. The applicant has also described a method of screening for antisense molecules. The example goes on to state that it well known in the art that a full-length antisense nucleic acid has inhibitory activity as do fragments of the full-length antisense nucleic acid provided that the they match accessible regions of the target nucleic acid. In consideration of the description provided by the applicant in Example 15, the Training

Materials go on to state that, in view of the level of knowledge in the art, a skilled artisan would recognize that the applicant possessed the genus embraced by a claim drawn to all antisense nucleic acids complementary to SEQ ID NO: 1 which inhibit HGH production, because the applicant has disclosed a full-length HGH sequence, a functional characteristic of the antisense nucleic acids (the inhibitory function) and a method of screening for such antisense nucleic acids. Accordingly, the Training Materials state that the claim in Example 15 is adequately described.

Like the applicants in Example 15 of the training materials, Applicants have described the full-length *waa*E coding nucleic acid (SEQ ID NO: 165) and its complement. In addition to the full-length antisense, Applicants describe two antisense fragments (SEQ ID NOs: 459 and 460) that are complementary to at least a portion of *waa*E and which inhibit cellular proliferation. Applicants also describe a method of screening for additional antisense nucleic acids having activity against the *waa*E gene and products thereof. In particular, Applicants describe a method for introducing an antisense nucleic acid into a cell and determining the extent of the inhibition of cellular proliferation that results (see Example 1 at page 31, lines 18 to 31). Applicants further describe the isolation and characterization of antisense nucleic acids that are determined to have proliferation-inhibiting activity (see Examples 1 and 2 at page 32, lines 1 to 15) and also provide numerous antisense nucleic acids comprising at least, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400 or 500 consecutive nucleotides of a sequences complementary to SEQ ID NO: 165 or complementary to a nucleotide sequence encoding a protein of SEQ ID NO: 325 which can be screened for activity against the *waa*E gene and it products using the above method (page 24, line 26 to page 25, line 20). It is readily appreciated within the art that antisense nucleic acid fragments of any size which correspond to at least a portion of the *waa*E gene can be assayed for the ability to inhibit cellular proliferation. In view of Example 15 of the Training Materials and the requirements of 35 U.S.C. § 112, first paragraph, discussed above, Applicants maintain that a sufficient description of claims 5-7 and 12-14 has been provided.

In view of the above arguments, Applicants submit that the instant specification provides adequate written description for each of the currently pending claims (claims 1-20). Accordingly, Applicants respectfully request that the Examiner withdraw his rejection of claims 1-20 under 35 U.S.C. § 112, first paragraph.

Claim Rejections Based on 35 U.S.C. § 112, first paragraph with Respect to Enablement

Claims 1-20 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled by the specification of the instant application. In his Office Action, the Examiner acknowledges that the broadest claims are drawn to any method of inhibiting cellular proliferation by inhibiting the activity or reducing the amount of a polypeptide of SEQ ID NO: 325 (WaaE) or inhibiting the activity or reducing the amount of a nucleic acid encoding this polypeptide. The Examiner also acknowledges that, in their specification, Applicants provide results which indicate that cellular proliferation of four different organisms was inhibited *in vitro* by providing either of two specific antisense molecules (SEQ ID NOs: 459 and 460) which are complementary, at least in part, to a gene which encodes the WaaE protein (SEQ ID NO: 325). In consideration of these results, the Examiner asserts that the claims are not adequately enabled with respect to methods of inhibiting proliferation of any organism, both *in vitro* and *in vivo*, by providing an antisense nucleic acid or any other compound that inhibits the activity or reduces the amount of a WaaE polypeptide or a nucleic acid encoding such polypeptide.

Applicants respectfully submit that claims 1-20 are adequately enabled by the specification of the instant patent application. In the discussion that follows, Applicants will address each of the aspects of the Examiner's enablement rejection. However, before addressing each of these issues, Applicants would like to take this opportunity to again point out that the claimed invention stems from the Applicants' discovery that the *waa*E gene and its gene products are required for cellular proliferation. As such, methods of inhibiting cellular proliferation that are based on this discovery can be enabled by providing sufficient disclosure that, in combination with the knowledge in the art, would allow a skilled artisan to practice the invention over the entire scope of the claim without undue experimentation. Applicants again note that, as discussed above, numerous patents have issued which claim the use of a broad class of compounds to achieve a particular biological result where the applicants were the first to appreciate that compounds sharing a particular mechanism of action could be used to obtain the biological result and that such patents were not required to set forth a long list of particular compounds which fall within the claimed class.

The enablement rejection set out in the Office Action is based on the Examiner's analysis of several factors that are set out in *In re Wands*. One aspect of the Examiner's enablement rejection is based on the assertion that the claims cover both *in vivo* and *in vitro* methods of

inhibiting cellular proliferation but the experimental data that is provided in the specification only demonstrates inhibition of proliferation *in vitro*. Another aspect of the Examiner's enablement rejection is based on the alleged unpredictability of methods of using antisense nucleic acids to inhibit cellular proliferation. In addition to the above, the Examiner asserts that Applicants have not disclosed the results of proliferation experiments from a sufficient number of organisms or with a sufficient number of compounds. Finally, even though the Examiner acknowledges that there exists a high level of skill in the art, he alleges that a skilled artisan would be required to perform substantial additional experimentation to determine (1) the compounds that could be used in the claimed methods; (2) the effect of these compounds on all possible organisms; (3) the efficacy of the compounds in treating animals infected with bacterial cells.

Applicants respectfully submit that the specification of the instant application provides ample guidance which would enable one skilled in the art to practice the claimed invention over the entire scope of each of the pending claims. For example, in addition to the antisense molecules already provided (SEQ ID NOs: 459 and 460), Applicants have disclosed detailed instructions in the specification for identifying additional compounds which can be used to inhibit cellular proliferation in accordance with the claimed invention. Although the Examiner asserts that it would take a considerable effort to identify compounds that inhibit proliferation using the disclosed procedure, Applicants respectfully point out that "a considerable amount of experimentation is permissible, if it is merely routine, or the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1359 (Fed. Cir. 1998); *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988); M.P.E.P. §2164.06). The instant specification provides extensive guidance regarding the screening of both combinatorial chemical and natural product libraries, the construction of which is well known in the art, to identify compounds that inhibit cellular proliferation by either inhibiting the activity or reducing the amount of a specific polypeptide, such as WaaE, or gene encoding such polypeptide. In particular, Example 8 describes both protein based assays, for identifying compounds that have activity against WaaE polypeptides, and cell based assays, which are use to identify compounds that have activity against either the *waa*E gene and/or its products (see Example 8, at pages 67, line 18 to 76, line 9). Example 9 provides a working example which verifies the effectiveness and specificity of the

cell based assay for identifying compounds which inhibit proliferation by acting on a gene, such as *waa*E, or its gene products (see Example 9, at page 76, line 10 to page 79, line 26). Applicants maintain that the foregoing disclosures enable those skilled in the art to practice the claimed invention without undue experimentation. Accordingly, Applicants have enabled those skilled in the art to identify and use compounds having activity against the *waa*E gene and its products in accordance with the claimed methods.

The Examiner also asserts that a skilled artisan must identify the organisms which fall within the scope of the claims. Applicants note that they have provided results which demonstrate that the proliferation of at least four different organisms can be inhibited by providing either of two antisense nucleic acids that is complementary to at least a portion of that gene. Other organisms that possess a *waa*E gene can be identified by a routine sequence homology comparison or by introducing antisense nucleic acids complementary to a portion of the *waaE* gene as described in the application. Applicants have provided detailed instructions that would permit a skilled artisan to inhibit proliferation by reducing the activity or reducing the amount of the WaaE protein or a nucleic acid encoding the protein. For example, the specification at page 59, lines 11 to 61 describes a method of "knocking out" the *waa*E gene by integrative gene replacement. In such methods, a disrupted copy of the *waa*E gene is provided to the organism and allowed to recombine with the chromosomal, wildtype copy of *waa*E. Upon cell division, the wildtype copy of *waa*E is lost leaving only the disrupted copy of this gene. Because a functional copy of the *waa*E gene is required for proliferation, all of the progeny cells, each which possess the disrupted copy of the *waa*E gene, fail to proliferate. In addition to the above-described method, Applicants have described methods of inhibiting cellular proliferation by down regulating the expression of the *waa*E gene (see page 62, lines 8-32) as well as the methods based on antisense technology (see Example 1 and throughout application). Accordingly, Applicants have enabled a skilled artisan to inhibit the proliferation of any organism the possesses a *waa*E gene.

Another aspect of the Examiner's enablement rejection relates to the antisense specific embodiments of the claimed invention. In particular, the Examiner asserts that there are several problems with the use of antisense molecules for the treatment of animals and/or humans. More specifically, the Examiner states that unmodified DNAs and RNAs are rapidly degraded by the

human body and long antisense nucleic acids have the potential for non-specific binding to non-target molecules.

Many of the foregoing assertions seem to be general concerns with the use antisense nucleic acids as therapeutics and with delivery of antisense nucleic acids. In this regard, while Applicants realize that actions taken by the P.T.O. in other patent applications are not binding on the P.T.O. with respect to the present application, Applicants note that a number of patents claiming the use of antisense nucleic acids as therapeutics and methods for delivering antisense nucleic acids have recently issued, thereby demonstrating that such inventions are not beyond the ability of those skilled in the art to make and use. (See attached U.S. Patent Nos. 6,524,854, 6,545,048 and 6,503,533.

In addition, Applicants respectfully submit that the above-mentioned issues have either been addressed by the instant specification or are not relevant to the invention as claimed. In addition to the working examples, which describe the use of specific antisense nucleic acids to mediate *in vitro* inhibition of cellular proliferation, Applicants have described a number of methods which allow a skilled artisan to stabilize antisense molecules for use *in vivo*. For example, the specification describes nucleotide modifications which can be used to increase the half life of antisense nucleic acids (see page 103, lines 8-13). Additionally, the specification describes both methods of making synthetic antisense nucleic acids having modified backbones which increase molecular stability (see page 102, line 26 to page 103, line 7) as well as methods for generating PNA analogs of specific antisense nucleic acids which are stabilized against degradation (see page 103, line 14 to page 104, line 19). The tools required to synthesize any of the above-mentioned stabilized antisense nucleic acid analogs are readily available and the knowledge to implement such syntheses is prevalent in the art.

With respect to the Examiner's statements regarding lack of specific binding by certain antisense nucleic acids, Applicants respectfully submit that absolute specificity of antisense binding is not a requirement of the claimed invention. The Examiner asserts that mismatches between the antisense nucleic acid and its target may result in the antisense nucleic acid binding to nucleic acids other than the target. Applicant notes that those skilled in the art can readily prepare antisense nucleic acids which do not have mismatches with their targets. Furthermore, since the intended effect of the antisense nucleic acids is to prevent proliferation, any adverse

effects on proliferation which might occur if the antisense nucleic acid did in fact bind to nucleic acids in addition to the target nucleic acid would be beneficial.

In view of the foregoing arguments, Applicants respectfully submit that all pending claims are enabled for methods of inhibiting cellular proliferation by providing antisense nucleic acids which are active against the *waa*E gene or products thereof.

Finally the Examiner states Applicants supply no data which would enable the *in vivo* applications of the claimed methods. In this respect, Applicants submit that the instant specification provides adequate guidance to enable a skilled artisan to practice the claimed methods *in vivo*. In particular, Applicants have provided Example 42 which describes how to administer an antisense nucleic acid to a patient in order to treat an infection (see page 107, lines 1-11). Applicants also describe methods that can be used to calculate a suitable antisense dose for use *in vivo* (see page 105, line 23 to page 106, line 6). Additionally, methods of formulating pharmaceutical compositions of antibiotic compounds, including antisense nucleic acids, are well known to those skilled in the art. Thus, a skilled artisan could practice the claimed methods *in vivo* without undue experimentation.

In view of the foregoing arguments, Applicants maintain that claims 1-20 are enabled by the specification as filed. Accordingly, Applicants respectfully request that the Examiner withdraw his rejection of claims 1-20 under 35 U.S.C. § 112, first paragraph..

CONCLUSION

Applicants believe that all outstanding issues in this case have been resolved and that the present claims are in condition for allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is invited to contact the undersigned at the telephone number provided below in order to expedite the resolution of such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: May 16, 2003

By: _____

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